201-15755A

# HIGH PRODUCTION VOLUME (HPV)

# CHEMICALS CHALLENGE PROGRAM



## TEST PLAN

## For

## TETRAHYDROBENZALDEHYDE

## CAS NO. 100-50-5

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**Prepared by:**

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# EXECUTE SUMMARY

The Dow Chemical Company voluntarily submits the following screening information data and Test Plan covering the chemical Tetrahydrobenzaldehyde, also known as THBA (CAS No. 100-50-5), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program. A substantial amount of data exists to evaluate the potential hazards associated with THBA. Use of key studies or estimation models available from data already developed provide adequate support to characterize all but three endpoints in the HPV Chemicals Challenge Program. The three endpoints for which no data presently exists are algal toxicity and developmental and reproduction toxicity. Modeling predicts that algae would be less affected than fish and daphnids by THBA. An algae study is considered to be unnecessary since THBA is a closed system intermediate. Any material accidentally released to the environment would be readily biodegraded. Since THBA is a closed system intermediate there is no need for a reproduction study. Based on the limited exposure of workers to this material and the corrosive nature of THBA which has resulted in a high degree of personal protective equipment, a developmental toxicity study is considered to be unnecessary.

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CAS Nos. 100-50-5

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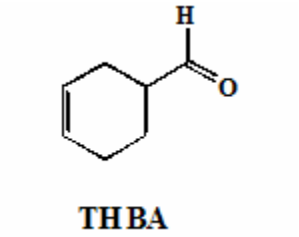
## I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, The Dow Chemical Company (Dow) has committed to voluntarily compile basic screening data on Tetrahydrobenzaldehyde (THBA). The data included in this Test Plan include physicochemical properties, environmental fate, and human and environmental effects of THBA, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed by or on behalf of Dow, or is found in the published scientific literature.

### A. Structure and Nomenclature

Following is a structural characterization of THBA and its associated nomenclature.




**THBA**

Tetrahydrobenzaldehyde
CAS No. : 100-50-5
Synonyms: THBA

### B. Manufacturing & Use

Union Carbide Corporation, a subsidiary of The Dow Chemical Company, operates a single manufacturing site producing THBA. The manufacturing operation is a closed, batch process. During production, butadiene and acrolein react together using a catalyst to produce THBA. Following the reaction, THBA is piped directly to another plant were it is used as a chemical intermediate. This material has been infrequently transported to a second UCC site (on average approximately once every two years) where it is also used as a chemical intermediate to produce a second product.

The Occupational Safety and Health Administration (OSHA) has set Permissible Exposure Limits (PEL) for the precursors 1,3-butadiene and acrolein of 1 and 0.1 ppm, respectively. Since 1,3-butadiene is a gas at room temperature, any production practices in place to limit exposure to 1,3-butadiene will be equally or more effective for reducing exposure to the relatively non-volatile THBA.

THBA has an odor threshold of approximately 0.22 ppm, and will be detected by smell before air concentrations reach unsafe levels.

Approximately 50 individuals are involved in the manufacture or use of THBA and these individuals have extremely low potential for skin and airborne exposure. Due to the subacute hazards associated with exposure to THBA, an occupational exposure limit of 5 ppm (Union Carbide Occupational Exposure Guideline) has been set. This has resulted in specific manufacturing procedures and practices to minimize the exposure potential to THBA. Between 1988 and 1998, over 300 samples were obtained from the THBA production and use plants. Only two values were greater than 1 ppm, and both of these were below the UCC Occupational Exposure Guideline. A review of more recent industrial hygiene samples from 1999 to the present in both manufacturing and use facilities have also shown that all samples are 1 ppm or lower. Due to the corrosive nature of THBA, personal protective equipment including (self-contained breathing apparatus (SCBA) when vapor exposure is high (considered to be greater than the action level (2.5 ppm) of the UCC Occupational Exposure Guideline), monogoggles, gloves and chemical apron, are worn whenever exposure to THBA is possible. Such operations could include sampling and material transfer operations, shutdown and clean-up activities.

Following the production of THBA, the material undergoes two chemical reactions to produce a single final product. The amount of THBA present in the final product is expected to be very low, probably less than 1 ppm.

The most likely but infrequent route of THBA emission would be via incorporation into wastewaters associated with its manufacture. These wastewaters are treated at an on-site wastewater treatment plant employing secondary biological treatment. Based on the ready biodegradability of THBA, the material is expected to be completely removed from wastewater during such treatment.

## II. TEST PLAN RATIONALE

The information included in this Test Plan has come from one or more of the following sources:
1) Internal studies conducted by or on behalf of The Dow Chemical Company
2) Studies that have been extracted from the scientific literature either as primary references, or as reported in well-accepted, peer-reviewed reference books
3) Calculation methods or quantitative structure-activity relationships (QSAR) \which are accepted by the US EPA for such purposes (1999b).

This assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with THBA. The data used to support this program include those Endpoints identified by the US EPA (1998). Key studies have been identified for each data Endpoint, and are summarized in Robust Summary form in Section VII of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:
1. Valid without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,
2. Valid with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary

slightly from current testing guidance. Also included are physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).
3. Not Valid – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.
4. Not Assignable – Includes studies in which limited data is provided.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Test Plan?.

## III. TEST PLAN SUMMARY AND CONCLUSIONS

**Physical-chemical property** values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were considered to be acceptable. The Vapor Pressure at 25$^{o}$ C (2.97 hPa) was calculated using an accepted estimation method, which accurately estimates the vapor pressure measured at a higher temperature (164° C). The Partition Coefficient was estimated using two different structure-fragment calculation methods, yielding Log Kow values of 1.34 and 1.89. The preferred, more conservative Log Kow value of 1.89 was determined using the accepted EPI Suite method.

Ref for VP is: AIChE. 2002. Design Institute for Physical Properties Research (DIPPR) Database, American Institute of Chemical Engineers, New York, NY.
Ref for EPI Suite is: U.S. EPA. 2003. EPI Suite software, version v3.11. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

**Environmental Fate** values for Hydrolysis, Photodegradation, and Transport (Fugacity) were obtained using computer estimation –modeling programs. The material is not expected to hydrolyze. The fugacity model predicts that emissions to water, the most likely emission scenario, will remain in water (99.9%). Any material that is released to the air will be rapidly photodegraded via reaction with hydroxyl radical and ozone. The predicted half life in the atmosphere is approximately 45 minutes (0.7 hr.). Biodegradation data were considered to be acceptable. THBA was shown to be readily biodegradable, using a test procedure which is equivalent to OECD Test Guideline 301D.

**Ecotoxicity** of THBA has been evaluated for several aquatic organisms. In the 14-day fish toxicity study the $LC_{50}$ was 1.1 mg/L. The $EC_{50}$ was much higher for daphnids, at 130 mg/L. The predicted $EC_{50}$ value for algae is greater than that predicted for fish and daphnids.

Blinova (2003) has examined freshwater bioassay organisms (e.g., algae, daphnia, and duckweed) and compared their relative acute sensitivities to a variety of water pollutants. She reported (http://www.mantraeast.org/pdf/use_of_bioassays.pdf) that acute studies with the freshwater algae, *Selenastrum capricornutum*, had equal or less sensitivity than acute studies with the daphnid (*Daphnia magna*) for leakage from oil-shale ash, industrial wastewater before treatment, and municipal wastewater before and after treatment; only sludge from the treatment plant was slightly more toxic to the algae than acute studies with the daphnid.

The Danish EPA has recently compared the QSAR vs. measured environmental toxicity data for 180 chemicals evaluated as part of the OECD HPV program. They report that >80, 75 and 65% of the

QSAR values were within a factor of 10 of the actual values for fish, daphnia and algae, respectively. Since the QSAR for THBA predicts the acute toxicity is lowest for algae and the Danish EPA have reported a good correlation between predicted and actual values, this confirms Blinova's assessment.

In consideration of the ready biodegradability of THBA, the low potential for environmental emission, and the less sensitivity predicted for algae, conducting an algae study is unnecessary.

**Mammalian Toxicity** Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing) have all been considered adequate. The material is very irritating and is corrosive in the dermal DOT test. When tested with a smaller amount of material than currently required in the eye irritation assay, 0.005 ml, moderately severe corneal injury was observed. Several two week studies have been conducted via two different routes. As part of these studies, the testes and ovaries were weighed and testes examined histopathologically. However, for reproductive toxicity purposes, these studies were of short duration and therefore rated a 4 in the Klimisch rating system. Although the study was of a short duration, there were no significant treatment-related effects noted which would indicate a reproductive effect. No developmental toxicity study was found. Point mutation and chromosomal aberration assays have been conducted and were uniformly negative.

A tabular depiction of data availability and testing recommendations for Tetrahydrobenzaldehyde (THBA) can be found in Table 1.

## IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and are further discussed below. Robust Summaries for each study referenced can be found in Section VII of this dossier.

### A. Chemical/Physical Properties

All measurable HPV Endpoints for Chemical/Physical Properties have been completed (Table 2). Widely divergent melting and boiling point values were cited in reputable sources. These values have been evaluated by a group from the American Institute of Chemical Engineers and summarized in the Design Institute for Physical Property Data (DIPPR®) database. A melting point of -96.1$^{o}$ C and a boiling point of 164$^{o}$ C were considered to be the most reliable. A vapor pressure of 2.97 hPa at 25 $^{o}$C was calculated from available data. Thus a saturated vapor contains approximately 2930 ppm at 25 $^{o}$C and 1000 hPa (750 mm Hg). The partition coefficient (Log Kow) was calculated to be 1.89. The material is reported to be slightly soluble in water (0.5% wt.).

### B. Environmental Fate and Biodegradation

All HPV Endpoints for Environmental Fate have been completed (Table 3). THBA has no hydrolysable functional groups. In air, THBA is expected to readily degrade via reaction with hydroxyl radicals and ozone. The half life in air is approximately 45 minutes. THBA is readily biodegradable, and will therefore be rapidly degraded in soil, surface waters, and sediments. A Level III fugacity model, simulating emission of 1,000 kg/hr. to water, predicts that nearly 99.9% of the emitted THBA will remain in the water compartment.

### C. Aquatic Toxicity

Aquatic toxicity data is available for the fish and daphnid (Table 4). The 14 day $LC_{50}$ for the guppy is 1.1 mg/L, and the 48 hr $EC_{50}$ for the daphnid is 130 mg/L. Predicted acute ecotoxicity values were calculated using the aldehyde class in the ECOSAR v0.99g program. Predicted 96 hour $LC_{50}$ values in the fish are approximately 10 fold greater than the actual 14 day $LC_{50}$ value. Conversely the predicted 48 hr $LC_{50}$ value in the daphnid is approximately 20 fold lower than the actual 48 hr EC50 value. Although no actual data is available for algae, the predicted value is approximately an order of magnitude greater than for the fish and daphnid. Based on both predicted and measured ecotoxicity, fish are expected to be the most sensitive to THBA. Thus, an algal toxicity study is considered to be unnecessary.

## D. Mammalian Toxicity Endpoints

Summaries of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity are found in Tables 5-7. Each of the Key Studies has been further summarized in the Robust Summary section of this Dossier.

### 1.0 Acute Toxicity

The acute oral and dermal $LD_{50}$ values are 2,385 mg/kg and 1,716 mg/kg, respectively. The 6 hour $LC_{50}$ is >1,679 ppm. The material was corrosive to the skin in a DOT study, and caused moderately severe corneal injury following application of 0.005 ml test material. This is a much lower dose than required in current guidelines. Thus the effect would be expected to be more severe if 0.1 ml test material had been used.

Due in part to the corrosive nature of THBA, protective equipment is required whenever contact with THBA is possible.

### 2.0 Repeated Dose Toxicity

Two separate two-week inhalation toxicity studies, as well as a two-week dermal toxicity study have been conducted with THBA (Table 6). Doses causing severe irritation at the application site in the dermal study produced only slight effects (mineral deposits) in the kidney. Inhalation exposure to THBA resulted in histopathologic changes in the nasal tissues. In these same animals, clinical changes in kidney function were observed, which included decreases in urine volume, pH and osmolality. However, there was no evidence of histopathologic changes. Thus, following the two most likely routes of exposure for humans, only minimal changes were observed at levels which resulted in severe irritation at the portal of entry.

### 3.0 Developmental Toxicity

There is no available developmental toxicity study (Table 6). However due to the corrosive nature of the material resulting in an increased level of personal protective equipment required ,the limited number of individuals exposed to THBA and the low concentrations measured in the workplace, a developmental toxicity study is considered to be unnecessary.

### 4.0 Reproductive Toxicity

There is no available reproduction toxicity study (Table 6). Several two week studies have been conducted via two different routes. As part of these studies, the testes and ovaries were weighed and testes examined histopathologically. However, for reproductive toxicity purposes, these studies were of

short duration and therefore rated a 4 in the Klimisch rating system. Although the study was of a short duration and produced severe irritation at the dermal application site and slight effects in the kidney, there were no significant treatment-related effects noted which would indicate a reproductive effect. Since the material is used solely as a chemical intermediate with limited worker exposure, a reproductive toxicity study is considered unnecessary.

## 5.0 Mutagenicity and Chromosomal Aberrations

### 5.1 Mutagenicity Testing (Ames test)

THBA was negative in the Ames test.

### 5.2 - Chromosomal Aberrations

THBA was negative in the in vitro CHO/HGPRT assay and in the in vivo mouse micronucleus assay.

No additional studies are necessary.

## V. REFERENCES

ACGIH TLV (2002). Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists.

Klimisch, H.-J., Andreae, M. and Tillman, U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

US EPA, (1998). Guidance for meeting the SIDS requirements (The SIDS Guide). Guidance for the HPV Challenge Program (11/31/98).

US EPA, (1999a). Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, (1999b). The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

## VI. ROBUST STUDY SUMMARIES -IUCLID

Data Sets are appended

# Table 1. Test Plan Matrix for TETRAHYDROBENZALDEHYDE

| | Info available? | OECD? | GLP? | Other study? | Estimated method? | Acceptable? |
|---|---|---|---|---|---|---|
| PHYSICAL CHEMICAL | | | | | | |
| Melting Point | Y | | | | N | Y |
| Boiling Point | Y | | | | N | Y |
| Vapor Pressure | Y | | | | N | Y |
| Partition Coefficent | Y | | | | N | Y |
| Water Solubility | Y | | | | N | Y |
| ENVIRONMENTAL FATE ENDPOINTS | | | | | | |
| Photodegradation | N | - | - | - | Y | Y |
| Hydrolysis | N | - | - | - | Y | Y |
| Biodegradation | Y | C | N | N | N | Y |
| Transport between Environmental Compartmenats (Fugacity) | N | - | - | - | Y | Y |
| ECOTOXICITY | | | | | | |
| Acute Toxicity to Fish | N | N | ND | Y | Y | Y |
| Acute Toxicity to Aquatic Invertebrates | Y | C | ND | N | Y | Y |
| Acute Toxicity to Aquatic Plants | N | - | - | - | Y | Y |
| MAMMALIAN TOXICITY | | | | | | |
| Acute Toxicity | Y | Y | Y | N | N | Y |
| Repeated Dose Toxicity | Y | Y | Y | N | N | Y |
| Genetic Toxicity - Mutation (Ames) | Y | Y | Y | N | N | Y |
| Genetic Toxicity - Chromosomal Aberrations | Y | Y | Y | N | N | Y |
| Developmental Toxicity | N | - | - | - | N | - |
| Reproductive Toxicity | N | - | - | - | N | - |

Y = Yes; N = No; C = Comparable; ND = No Data; S = Supplemental, not required under HPV; - = Not applicable

## Table 2. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

### Physicochemical Properties

| Name (CAS No.) | Melting Point ($^{o}$C) | Vapor Pressure (hPa @ 25$^{o}$C) | Boiling Point ($^{o}$C) | Partition Coefficient (log Kow) | Water Solubility (mg/L @ 20C) |
|---|---|---|---|---|---|
| TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) | -96.1 (measured) | 2.97 (2.225 mm Hg) (calculated) | 164 (measured) | 1.89 (preferred calc.) 1.34 ( other calc.) | 0.5% Slightly soluble (measured) |

# Table 3. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

## Environmental Fate

| **Name (CAS No.)** | **Hydrolysis** | **Photodegradation** Half life | **Biodegradation** | **Environmental Transport** Level III, 1000 kg/hr released to water |
|---|---|---|---|---|
| TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) | Not estimatable (Hyrowin 1.67) Does not contain hydrolyzable groups | Hydroxyl Radicals Reaction: 88.6330 E-12 Ozone Reaction: 20.000000 E-17 cm3/molecule-sec Overall half life = 0.7 hours | readily biodegradable 76% in a closed bottle test equivalent to OECD 301D | Air 0.035% Water 99.9% Soil 0.0033% Sediment 0.074% |

# Table 4. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

## Ecotoxicity

| Name (CAS No.) | Acute Fish 96-hour LC50 (mg/L) | Acute Invertebrate 48-hour EC50 (mg/L) | Algal 72-hour growth inhibition EC50 (mg/L) |
|---|---|---|---|
| TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) | No data for acute study<br>Predicted 96 hr LC50 9.997 mg/L<br>Chronic 14-day LC50 is 1.1 mg/L<br>Predicted 32-day Chronic Value (ChV) is 0.885 mg/L | 130<br>Predicted 48 hr LC50 6.85 mg/L | No data for acute study<br>Predicted 96 hr EC50 68.4 mg/L |

# Table 5. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

## Acute Toxicity

| Name (CAS No.) | Acute Oral | Acute Dermal | Acute Inhalation | Dermal Irritation | Eye Irritation | Sensitization |
|---|---|---|---|---|---|---|
| TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) | 2385 mg/kg | 1716mg/kg | >1679 ppm for 6 hour exposure | Corrosive according to DOT test | Moderately severe corneal injury using 0.005 ml test material | No data |

# Table 6. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

## Repeat-dose Toxicity

| Name (CAS No.) | Repeat Dose | Reproductive | Developmental |
|---|---|---|---|
| TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) | Two week inhalation NOEL – 5 ppm<br>Two week dermal systemic NOEL – 0.10 ml/kg/day | No effect on ovary or testicular weights or testes histopath in two week dermal study | No data |

# Table 7. Matrix of Available and Adequate Data on TETRAHYDROBENZALDEHYDE

## Genotoxicity

| **Name (CAS No.)** | **Genotoxicity (*in vitro* -bacterial)** | **Genotoxicity (*in vitro* - mammalian)** | **Genotoxicity (*in vivo*)** |
|---|---|---|---|
| TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) | Negative | Negative in CHO/HGPRT assay | Negative in mouse micronucleus assay |

## Table 8 Test Plan Matrix for TETRAHYDROBENZALDEHYDE

| | TETRAHYDROBENZALDEHYDE (THBA) (100-50-5) |
|---|---|
| **PHYSICAL CHEMISTRY** | |
| Melting point, °C | -96.1 (measured)<br>A |
| Boiling point, °C | 164 (measured)<br>A |
| Vapor Pressure, hPa at 25C | 2.97 (calculated)<br>A |
| Water Solubility | 0.5% (measured)<br>Slightly soluble<br>A |
| Log $K_{ow}$ | 1.89(calculated)<br>A |
| **ENVIRONMENTAL FATE** | |
| Biodegradation | 76% in closed bottle test equivalent to OECD 301D<br>readily biodegradable<br>A |
| Hydrolysis | Does not contain hydrolysable groups<br>A |
| Photodegradability | Overall half life = 0.7 hours<br>A |
| Transport between Environmental Compartments:<br>(**Fugacity Level III Model**) Default assumption: 1000 kg/hr released into water. | Air 0.035%<br>Water 99.9%<br>Soil 0.0033%<br>Sediment 0.074%<br>A |
| **ECOTOXICITY** | |
| Chronic Toxicity to Fish (14 day LC50) | 14-day is 1.1 mg/L (measured)<br>A |
| Acute Toxicity to Aquatic Invertebrates (48hr EC50) | 130 (measured)<br>A |
| Toxicity to Aquatic Plants (72hr EC50) | 68.4 (calculated) |
| **TOXICOLOGICAL DATA** | |
| Acute Toxicity (oral), mg/kg | 2385 mg/kg<br>A |
| Acute Toxicity (dermal) mg/kg | 1716 mg/kg<br>A |
| Acute Toxicity (inhalation) | > 1679 ppm for 6 hour exposure<br>A |

| | |
|---|---|
| Acute Eye Irritation | Moderately severe corneal injury using 0.005 ml test material<br>A |
| Acute Skin Irritation | Corrosive according to DOT test<br>A |
| Sensitization | No data<br>NR |
| Repeated Dose Toxicity | Two week NOEL – 5 ppm<br>A |
| Genetic Toxicity-Mutation | Negative<br>A |
| Genetic Toxicity- Chromosomal Aberrations | Negative (in vitro)<br>Negative (in vivo)<br>A |
| Toxicity to Reproduction | No data<br>NR |
| Developmental Toxicity | No data<br>NA |

| **Legend** | |
|---|---|
| **Symbol** | **Description** |
| R | Endpoint requirement fulfilled using category approach, SAR |
| Test | Endpoint requirements to be fulfilled with testing |
| Calc | Endpoint requirement fulfilled based on calculated data |
| A | Endpoint requirement fulfilled with adequate existing data |
| NR | Not required per the OECD SIDS guidance |
| NA | Not applicable due to physical/chemical properties |